

AMENDMENTS TO THE SPECIFICATION

On page 1, before the heading "FIELD OF THE INVENTION" please add the following paragraph:

-- This application is the National Stage of International Application No. PCT/EP2003/08725, filed on August 7, 2003. --

Please replace the paragraph beginning at line 20 on page 5 of the specification with the following amended paragraph:

-- The mature amino acid sequence of human EPO contains 166 amino acid residues and depicted in single-letter code comprises the following sequence:

APPRLICDSRVLERYLLEAKEAENITTGCAEHCSLNENITVPDTKVNFYAWKRMEVGGQAV
EVWQGLALLSEAVLRGQALLVNSSQPWEPLQLHVDKAVSGLRSLTTLRLALGAQKEAISPP
DAASAAPLRTITADTFRKLFRVYSNFLRGKCLKLYTGEACRTGDR (SEQ ID NO: 1). --

Please replace the paragraph beginning at line 23 on page 8 of the specification with the following amended paragraph:

-- an accordingly specified molecule wherein alteration is conducted at one or more residues from the string of contiguous residues defined herein as epitope regions and comprising one of the sequences

(a) RVLERYLLEAKEAENITTGCAEHCSLNENITVP (SEQ ID NO: 2; residues 10-42 of SEQ ID NO: 1),

(b) RGQALLVNSSQPWEPLQLHVDKAVSGLRSLTTL (SEQ ID NO: 3; residues 76-108 of SEQ ID NO: 1), or

(c) RTITADTFRKLFRVYSNFLRGKCLKLYTGEACRT (SEQ ID NO: 4; residues 131-163 of SEQ ID NO: 1); --

Please replace the paragraph beginning at line 29 on page 8 of the specification with the following amended paragraph:

-- an accordingly specified molecule wherein alteration is conducted at one or more residues from the string of contiguous residues defined herein as epitope region R1 and comprising the sequence AKEAENITTGCAEHCSLNENI (SEQ ID NO: 5; residues 19-39 of SEQ ID NO: 1); --

Please replace the paragraph beginning at line 1 on page 9 of the specification with the following amended paragraph:

-- an accordingly specified molecule wherein alteration is conducted at one or more residues from the string of contiguous residues defined herein as epitope region R2 and comprising the sequence RGQALLVNSSQPWEPLQLHVD (SEQ ID NO: 6; residues 76-96 of SEQ ID NO: 1); --

Please replace the paragraph beginning at line 4 on page 9 of the specification with the following amended paragraph:

-- an accordingly specified molecule wherein alteration is conducted at one or more residues from the string of contiguous residues defined herein as epitope region R3 and comprising the sequence TFRKLFRVYSNFLRGKCLKLYT (SEQ ID NO: 7; residues 137-157 of SEQ ID NO: 1); --

Please replace the paragraph beginning at line 1 on page 13 of the specification with the following amended paragraph:

-- Similarly the inclusion of control peptides for which there is expectation that the majority of PBMC donor samples will be responsive may be included in each assay plate. The influenza haemagglutinin peptide 307-309, sequence PKYVKQNTLKLA (SEQ ID NO: 8); and the *Chlamydia* HSP 60 peptide sequence KVVDQIKKISKPVQH (SEQ ID NO: 9) are particularly suitable control peptides although many other examples may be exploited. Assays should preferably also use a potent whole protein antigen such as hemocyanin from Keyhole Limpet to which all PBMC samples would be expected to exhibit an SI significantly greater than 2.0. --

Please replace Table 1 beginning after line 27 on page 14 of the specification with the following amended table:

PeptideID #	Residue *	<u>SEQ ID NO:</u>	Peptide Sequence
P4	10	<u>13</u>	RVLERYLLEAKEAEN
P7	19	<u>16</u>	AKEAENITTGCAEHC
P8	22	<u>17</u>	AENITTGCAEHCSLN
P9	25	<u>18</u>	ITTGCAEHCSLNENI
P10	28	<u>19</u>	GCAEHCSLNENITVP
P16	46	<u>25</u>	VNFYAWKRMEVGQQA
P26	76	<u>35</u>	RGQALLVNSSQPWEP
P27	79	<u>36</u>	ALLVNSSQPWEPLQL
P28	82	<u>37</u>	VNSSQPWEPLQLHVD
P32	94	<u>41</u>	HVDKAVSGLRSLTTL
P41	122	<u>50</u>	PDAASAAPLRTITAD
P44	131	<u>53</u>	RTITADTFRKLFRVY
P46	137	<u>55</u>	TFRKLFRVYSNFLRG
P47	140	<u>56</u>	KLFRVYSNFLRGKLG
P48	143	<u>57</u>	RVYSNFLRGKLGKLYT
P50	149	<u>59</u>	LRGKLGKLYTGEACRT

Please replace Table 2 on page 15 of the specification with the following amended table:

Peptide ID #	Residue #	<u>SEQ ID NO:</u>	Peptide Sequence	Epitope Region
P7	19	<u>16</u>	AKEAENITTGCAEHC	R1
P8	22	<u>17</u>	AENITTGCAEHCSLN	
P9	25	<u>18</u>	ITTGCAEHCSLNENI	
P26	76	<u>35</u>	RGQALLVNSSQPWEP	R2
P46	137	<u>55</u>	TFRKLFVYSNFLRG	R3
P47	140	<u>56</u>	KLFRVYSNFLRGKLG	
P50	149	<u>59</u>	LRGKLKLYTGEACRT	

Please replace the paragraph beginning at line 1 on page 16 of the specification with the following amended paragraph:

-- Epitope region R1 is encompassed by peptides P7, P8 and P9 comprising the sequence AKEAENITTGCAEHCSLNENI (SEQ ID NO: 5; residues 19-39 of SEQ ID NO: 1). Epitope region R2 is encompassed by peptide P26 comprising the sequence RGQALLVNSSQPWEP (SEQ ID NO: 35). Note that for the R2 epitope, successive peptides P27 and P28 are also reactive each with one PBMC donor sample. In the case of the P27 peptide the donor is also reactive to the P26 peptide and it is likely that a single common core sequence within R2 is responsible for this stimulation. Owing to the phasing of each successive peptide in the sequence, it is possible that the same core nonamer sequence is shared ([[i.e]] i.e., is common) between either 2 or 3 adjacent peptides. The exact phasing is dependent on proximity to the N-terminus and tied to the length of the peptides and number of “new” residues scanned by each successive increment of the sequence. In the case of the R2 epitope, the C-terminal boundary of the epitope region has been set to include sequence covered by peptides P27 and P28 not least as this region is shown to contain significant MHC class II ligands in its C-terminal region (see later and FIGURE 2). Epitope region R2 is accordingly defined by the sequence RGQALLVNSSQPWEPLQLHVD (SEQ ID NO: 6; residues 76-96 of SEQ ID NO: 1). --

Please replace the paragraph beginning at line 4 on page 26 of the specification with the following amended paragraph:

-- Epitope region R3 is encompassed by peptides P46 and P47 and extends toward the C-terminus of the EPO sequence. The C-terminal boundary of eptope R3 is limited by the natural terminus of the EPO protein, notably peptide P50 is also reactive in two donor samples and these donors are the same as react with peptides P46 and P47. The core of the R3 epitope is considered to comprise the sequence TFRKLFRVYSNFLRGKLLK (residues 137-154 of SEQ ID NO: 1), but an additional MHC class II ligand and known reactive peptide comprises the overlapping P50 peptide sequence LRGKLLKLYTGEACRT (SEQ ID NO: 59) to give a total R3 sequence comprising TFRKLFRVYSNFLRGKLLKLYT (SEQ ID NO: 7; residues 137-157 of SEQ ID NO: 1). --

Please replace the paragraph beginning at line 29 on page 22 of the specification with the following amended paragraph:

-- ~~FIGURE 1~~ FIGURE 1 is a depiction of the MHC class II ligands identified within epitope region R1 (SEQ ID NO: 5; residues 19-39 of SEQ ID NO: 1). Ligands are identified using the *in silico* system of EXAMPLE 2. In this case the binding profile of 18 human DR allotypes are displayed as columns. The ligands detected are 13-mers and residue number 1 of each 13-mer is identified by a coloured block. The intensity of the binding interaction (High, Medium or Low) for each peptide with respect to each of the 18 allotypes is indicated according to the key displayed. --

Please replace the paragraph beginning at line 3 on page 23 of the specification with the following amended paragraph:

-- ~~FIGURE 2~~ FIGURE 2 is a depiction of the MHC class II ligands identified within epitope region R2 (i.e., SEQ ID NO: 6; residues 76-96 of SEQ ID NO: 1). Ligands are identified using the *in silico* system of EXAMPLE 2. In this case the binding profile of 18 human DR allotypes are displayed as columns. The ligands detected are 13-mers and residue number 1 of each 13-mer is identified by a coloured block. The intensity of the binding interaction (High , Medium or Low) for each peptide with respect to each of the 18 allotypes is indicated according to the key displayed. --

Please replace the paragraph beginning at line 10 on page 23 of the specification with the following amended paragraph:

-- ~~FIGURE 3~~ FIGURE 3 is a depiction of the MHC class II ligands identified within epitope region R3 (i.e., SEQ ID NO: 7; residues 137-157 of SEQ ID NO: 1). Ligands are identified using the *in silico* system of EXAMPLE 2. In this case the binding profile of 18 human DR allotypes are displayed as columns. The ligands detected are 13-mers and residue number 1 of each 13-mer is identified by a coloured block. The intensity of the binding interaction (High , Medium or Low) for each peptide with respect to each of the 18 allotypes is indicated according to the key displayed. --

Please replace the paragraph beginning at line 17 on page 23 of the specification with the following amended paragraph:

-- ~~FIGURE 4~~ FIGURE 4 depicts a most preferred EPO structure (SEQ ID NO: 61) in which MHC class II ligands are eliminated by substitution within epitope regions R1, R2 and R3. --

Please replace the paragraph beginning at line 30 on page 24 of the specification with the following amended paragraph:

-- The control antigens used in this study were Flu haemagglutinin 307-319 (sequence: PKYVKQNTLKLAT; SEQ ID NO: 8); *Chlamydia* HSP 60 peptide (sequence: KVVDQIKKISKPVQH; SEQ ID NO: 9) and Keyhole Limpet hemocyanin. --

Please replace Table 3 on page 25 of the specification with the following amended table:

Peptide ID #	EPO; 15mer peptide sequence	SEQ ID NO:	Residue #
P1	APPRLICDSRVLERY	<u>10</u>	1
P2	RLICDSRVLERYLLE	<u>11</u>	4
P3	CDSRVLERYLLEAKE	<u>12</u>	7
P4	RVLERYLLEAKEAEN	<u>13</u>	10
P5	ERYLLEAKEAENITT	<u>14</u>	13
P6	LLEAKEAENITTGCA	<u>15</u>	16
P7	AKEAENITTGCAEHC	<u>16</u>	19
P8	AENITTGCAEHCSLN	<u>17</u>	22
P9	ITTGCAEHCSLNENI	<u>18</u>	25
P10	GCAEHCSLNENITVP	<u>19</u>	28
P11	EHCSLNENITVPDTK	<u>20</u>	31
P12	SLNENITVPDTKVNF	<u>21</u>	34
P13	ENITVPDTKVNFYAW	<u>22</u>	37
P14	TVPDTKVNFYAWKRM	<u>23</u>	40
P15	DTKVNFYAWKRMEVG	<u>24</u>	43
P16	VNFYAWKRMEVGQQA	<u>25</u>	46
P17	YAWKRMEVGQQAVEV	<u>26</u>	49
P18	KRMEVGQQAVEVWQG	<u>27</u>	52
P19	EVGQQAVEVWQGLAL	<u>28</u>	55
P20	QQAVEVWQGLALLSE	<u>29</u>	58
P21	VEVWQGLALLSEAVL	<u>30</u>	61
P22	WQGLALLSEAVLRGQ	<u>31</u>	64
P23	LALLSEAVLRGQALL	<u>32</u>	67
P24	LSEAVLRGQALLVNS	<u>33</u>	70
P25	AVLRGQALLVNSSQP	<u>34</u>	73
P26	RGQALLVNSSQPWEP	<u>35</u>	76
P27	ALLVNSSQPWEPLQL	<u>36</u>	79
P28	VNSSQPWEPLQLHVD	<u>37</u>	82
P29	SQPWEPLQLHVDKAV	<u>38</u>	85
P30	WEPLQLHVDKAVSGL	<u>39</u>	88
P31	LQLHVDKAVSGLRSL	<u>40</u>	91
P32	HVDKAVSGLRSLTTL	<u>41</u>	94
P33	KAVSGLRSLTLLRA	<u>42</u>	97
P34	SGLRSLTLLRALGA	<u>43</u>	100
P35	RSLTLLRALGAQKE	<u>44</u>	103
P36	TLLRALGAQKEAIS	<u>45</u>	106
P37	LRALGAQKEAISPPD	<u>46</u>	109
P38	LGAQKEAISPPDAAS	<u>47</u>	112
P39	QKEAISPPDAASAAP	<u>48</u>	115
P40	AISPPDAASAAPLRT	<u>49</u>	118
P41	PDAASAAPLRTITAD	<u>50</u>	122
P42	ASAAPLRTITADTFR	<u>51</u>	125
P43	APLRTITADTFRKLF	<u>52</u>	128
P44	RTITADTFRKLFVY	<u>53</u>	131
P45	TADTFRKLFVYSNF	<u>54</u>	134
P46	TFRKLFVYSNFLRG	<u>55</u>	137
P47	KLFVYSNFLRGKLG	<u>56</u>	140
P48	RVYSNFLRGKLGKLYT	<u>57</u>	143
P49	SNFLRGKLGKLYTGEA	<u>58</u>	146
P50	LRGKLGKLYTGEACRT	<u>59</u>	149
P51	KLKLYTGEACRTGDR	60	152

Please replace Table 4 beginning on page 26 of the specification with the following amended table:

Peptide ID #	SEQ ID NO:	Peptide Sequence	Responsive Allotypes
P4	<u>13</u>	RVLERYLLEAKEAEN	DRB1*11, DRB1*0103, DRB3 DRB1*04, DRB1*07, DRB4*01
P7	<u>16</u>	AKEAENITTGCAEHC	DRB1*01, DRB1*08 DRB1*10, DRB1*13, DRB3 DRB1*01, DRB1*08
P8	<u>17</u>	AENITTGCAEHCSLN	DRB1*10, DRB1*13, DRB3 DRB1*11, DRB1*15, DRB3, DRB5 DRB1*01, DRB1*08
P9	<u>18</u>	ITTGCAEHCSLNENI	DRB1*10, DRB1*13, DRB3
P10	<u>19</u>	GCAEHCSLNENITVP	DRB1*01, DRB1*08
P16	<u>25</u>	VNFYAWKRMEVGQQA	DRB1*11, DRB1*0103, DRB3 DRB1*10, DRB1*13, DRB3
P26	<u>35</u>	RGQALLVNSSQPWEP	DRB1*11, DRB1*15, DRB3, DRB5
P27	<u>36</u>	ALLVNSSQPWEPLQL	DRB1*11, DRB1*15, DRB3, DRB5
P28	<u>37</u>	VNSSQPWEPLQLHVD	DRB1*10, DRB1*13, DRB3
P32	<u>40</u>	HVDKAVSGLRSLTTL	DRB1*04, DRB1*07, DRB4*01
P41	<u>50</u>	PDAASAAPLRTITAD	DRB1*15, DRB1*0103, DRB5
P44	<u>53</u>	RTITADTFRKLFRVY	DRB1*11, DRB1*0103, DRB3 DRB1*13, DRB1*14 or DRB1*14
P46	<u>55</u>	TFRKLFRVYSNFLRG	only, DRB3 DRB1*11, DRB1*0103, DRB3 DRB1*13, DRB1*14 or DRB1*14
P47	<u>56</u>	KLFRVYSNFLRGKLGK	only, DRB3 DRB1*11, DRB1*0103, DRB3
P48	<u>57</u>	RVYSNFLRGKLGKLYT	DRB1*11, DRB1*0103, DRB3 DRB1*13, DRB1*14 or DRB1*14
P50	<u>59</u>	LRGKLGKLYTGEACRT	only, DRB3 DRB1*11, DRB1*0103, DRB3

Please replace the paragraph beginning at line 17 on page 28 of the specification with the following amended paragraph:

-- An EPO structure containing the most preferred set of substitutions according to the above scheme is depicted below (SEQ ID NO: 61) and in FIGURE 4. --